

Prognostic significance of cardiac ^{123}I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: a prospective study

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Abstract

Objective—To determine whether cardiac iodine-123 metaiodobenzylguanidine (^{123}I MIBG) imaging is useful in predicting the prognosis of patients with chronic heart failure.

Design—Cardiac ^{123}I MIBG imaging was done on entry to the study. The cardiac MIBG washout rate was calculated from anterior chest view images obtained 20 and 200 minutes after injection of the isotope. Study patients were divided into two groups with washout rates above and below 27% (the mean value + 2 SD obtained in 20 normal subjects), and were then followed up.

Setting—Tertiary referral centre.

Patients—79 patients with chronic heart failure in whom the left ventricular ejection fraction was less than 40%.

Results—There were 37 patients in group 1 (washout rate of $\geq 27\%$) and 42 in group 2 ($< 27\%$). During a follow up period of between 1 and 52 months, eight patients died suddenly and five died of worsening heart failure in group 1, while none died in group 2; 13 patients in group 1 and four in group 2 were admitted to hospital for progressive heart failure. Kaplan-Meier analysis showed that group 1 had a significantly higher mortality and morbidity ($p = 0.001$ and $p < 0.001$, respectively) than group 2.

Conclusions—Cardiac ^{123}I MIBG washout rate seems to be a good predictor of prognosis in patients with chronic heart failure.

(Heart 2001;86:656-660)

Keywords: chronic heart failure; sudden death; cardiac adrenergic nerve activity

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Accepted 11 July 2001

Chronic heart failure is common and has a high mortality.¹ It would be clinically valuable to be able to identify patients most at risk of dying. In patients with chronic heart failure, cardiac adrenergic nerve function is characterised by reduction in noradrenaline (norepinephrine) uptake and acceleration of spillover in the myocardial adrenergic nerve terminals.^{2,3} This abnormality of adrenergic nerve function is an important factor determining the survival of patients with chronic heart failure.⁴

Cardiac adrenergic nerve activity has been estimated using iodine-123 metaiodobenzylguanidine (^{123}I MIBG) as a noradrenaline analogue.⁵ It has been reported that cardiac ^{123}I MIBG imaging has prognostic value in patients with chronic heart failure.⁶ Recent reports have shown that the heart to mediastinum ratio obtained during cardiac ^{123}I MIBG imaging is prognostically useful in patients with chronic heart failure or dilated cardiomyopathy.^{7,8} However, few data are yet available on whether the cardiac MIBG washout rate might also be useful as a prognostic index in patients with chronic heart failure. We therefore studied prospectively a group of patients with chronic heart failure to determine the relation between cardiac ^{123}I MIBG washout rate and subsequent mortality and morbidity.

Methods

STUDY PATIENTS

The participants consisted of 79 consecutive patients with chronic heart failure seen in our clinic. In all cases their left ventricular ejection fraction, measured by radionuclide angiography, was less than 40%. Forty five had ischaemic heart disease and the remaining 34 had idiopathic dilated cardiomyopathy. Their mean age was 64.1 years (range 28-85 years). There were 64 men and 15 women. At entry, all patients had cardiac ^{123}I MIBG imaging, echocardiography, and plasma noradrenaline assay.

All patients gave written informed consent for their participation in the study, which was approved by the Osaka Prefectural General Hospital review committee.

RADIONUCLIDE ANGIOGRAPHY FOR ENTRY CRITERIA

Before entering this study, patients underwent ECG gated blood pool scintigraphy at rest in the supine position, using a conventional rotating gamma camera (Prism 2000, Picker, Bedford, Ohio, USA) equipped with a low energy, high resolution parallel hole collimator. Patients were given 740 MBq of $^{99\text{m}}\text{Tc}$ labelled human serum albumin (Nihon Medi-Physics, Nishinomiya, Japan). The camera was positioned in the modified left anterior oblique projection to isolate the left ventricle from

other cardiac structures and data acquisition was then completed. The left ventricular ejection fraction was calculated using a standard program.⁹

CARDIAC ¹²³I MIBG IMAGING

No patients were taking tricyclic antidepressant drugs, sympathomimetic agents, or other drugs known to interfere with ¹²³I MIBG uptake in the month preceding the cardiac ¹²³I MIBG imaging.

Cardiac ¹²³I MIBG image acquisition

All patients underwent myocardial imaging with ¹²³I MIBG (Daiichi Radioisotope Laboratory, Tokyo, Japan) using the same gamma camera as for the radionuclide angiography. Patients were placed in the supine position. A 111 Mbq dose of ¹²³I MIBG was injected intravenously at rest after an overnight fast. Initial and delayed image acquisitions were performed in the anterior chest view 20 minutes and 200 minutes after the isotope injection.

Image analysis

Two independent observers, unaware of the clinical status of patients, assessed cardiac MIBG uptake. Left ventricular activity was recorded using a manually drawn region of interest (ROI) over the whole left ventricular myocardium, and mean heart counts per pixel were calculated. Another 7 × 7 pixel ROI was recorded over the upper mediastinal area, and the mean counts per pixel calculated. The heart to mediastinum (H:M) ratio was then determined from the cardiac ¹²³I MIBG images using the following formula: H:M ratio = [H]/[M], where [H] = mean counts per pixel in the left ventricle, and [M] = mean counts per pixel in the upper mediastinum. After taking radioactive decay of ¹²³I into consideration, the cardiac MIBG washout rate was calculated from initial and delayed images as follows:

$$\text{MIBG washout rate} = \frac{\left(\frac{[H]}{(1/2)^{t_1}} - \frac{[M]}{(1/2)^{t_1}} \right)_{\text{initial}} - \left(\frac{[H]}{(1/2)^{t_2}} - \frac{[M]}{(1/2)^{t_2}} \right)_{\text{delayed}}}{\left(\frac{[H]}{(1/2)^{t_1}} - \frac{[M]}{(1/2)^{t_1}} \right)_{\text{initial}}} \times 100(\%)$$

where T = half time of ¹²³I (13.3 hours); t₁ = time interval from isotope injection to measurement of the initial image (hours); and t₂ = time interval from isotope injection to measurement of the delayed image (hours).

ECHOCARDIOGRAPHIC EXAMINATION

Cross sectional echocardiography was performed with a Toshiba SSH-65A or 160A recorder equipped with 2.5 or 3.75 MHz transducers. The standard technique was employed for sizing the left ventricle and atrium.¹⁰ Left ventricular dimensions were measured at end diastole (LVDd) on the R wave of the ECG derived QRS complex, just below the level of the mitral leaflets, through the standard left parasternal window. The left atrial dimension was measured as the distance

from the leading edge of the posterior aortic wall to the leading edge of the posterior left atrial wall at the end systole.

PLASMA NORADRENALINE CONCENTRATION

After resting in the supine position for 30 minutes, blood was withdrawn into tubes containing EDTA. The plasma noradrenaline concentration was measured using high performance liquid chromatography¹¹ (Shionogi Biomedical Laboratories, Osaka, Japan). Duplicate determinations in the laboratory had a coefficient of variation of 0.4–5.5%.

STUDY PROTOCOL

Before this study, we determined a control value for cardiac MIBG washout rate in 20 volunteer subjects (10 men and 10 women) with normal cardiac function documented by echocardiography. Their mean (SD) age was 63.7 (11.5) years, mean ejection fraction 69.9 (7.6)%, and mean end diastolic left ventricular dimension 46.3 (6.5) mm. All gave their informed consent for their participation as controls. The mean cardiac MIBG washout rate obtained from these control subjects was 9.6 (8.5)%. We therefore adopted a value of 27%, which is the mean control washout rate +2 SD, as the cut off point for dividing the chronic heart failure patients into two groups: patients in group 1 had a washout rate of 27% and more, and those in group 2 had a washout rate of less than 27%.

All the study patients were then followed up in our hospital at least once a month by clinicians who did not know the results of the cardiac MIBG washout rate determinations. The end point of the study was either when a patient died suddenly (or from other cardiac diseases), or when a patient was admitted to hospital for worsening heart failure.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). To evaluate the difference between the two groups, we used the unpaired Student *t* test for continuous variables and the χ^2 test for discrete variables. For evaluation of the mortality and morbidity in the two groups, we used Kaplan–Meier analysis. The mortality and morbidity curves were compared by the log rank test. We also performed the multivariate analysis to determine which variable contributed most to the mortality and morbidity, using the Cox proportional hazard model. A probability value of *p* < 0.05 was regarded as significant.

Results

BASELINE AND PRESENTATION CHARACTERISTICS

Group 1, in which the MIBG washout rate was 27% or more, consisted of 37 patients; group 2, with a washout rate of less than 27%, consisted of 42 patients. In group 1, 20 patients had ischaemic heart disease and 17 had non-ischaemic heart disease; in group 2, 25 had ischaemic heart disease, and 17 had non-ischaemic heart disease. There were no significant differences between the two groups in age, sex, proportion with ischaemic heart disease,

Table 1 Baseline characteristics at the entry to the study in patients from group 1 and group 2

| Variable | Group 1 | Group 2 | p Value |
|-------------------------------|-------------|-------------|---------|
| n | 37 | 42 | |
| Age (years) | 65.5 (11.4) | 62.8 (11.5) | 0.289 |
| Sex (male/female) | 30/7 | 34/8 | 0.988 |
| Ischaemic heart disease | 20 (54.1%) | 25 (59.5%) | 0.624 |
| NYHA classification | 1.8 (0.6) | 1.9 (0.5) | 0.893 |
| Echocardiography | | | |
| LVDd (mm) | 63.9 (7.6) | 60.0 (6.3) | 0.016 |
| LAD (mm) | 44.0 (8.8) | 40.3 (6.3) | 0.034 |
| Radionuclide angiography | | | |
| EF (%) | 28.9 (8.4) | 29.7 (7.5) | 0.630 |
| Plasma noradrenaline (pg/ml) | 499 (252) | 344 (145) | 0.001 |
| ¹²³ I MIBG imaging | | | |
| H:M ratio on delayed image | 1.5 (0.2) | 1.9 (0.2) | < 0.001 |
| Washout rate (%) | 42.4 (10.0) | 16.4 (6.9) | < 0.001 |
| Drug treatment | | | |
| ACE inhibitor | 28 (75.7%) | 32 (76.2%) | 0.957 |
| β Blocker | 8 (21.6%) | 12 (28.6%) | 0.478 |

Data are n, n (%), or mean (SD).

ACE, angiotensin converting enzyme; EF, ejection fraction; H:M, heart to mediastinum; LAD, left atrial dimension; LVDd, left ventricular end diastolic dimension; MIBG, metaiodobenzylguanidine; NYHA, New York Heart Association.

Table 2 Follow up outcome of the study patients

| Outcome | Group 1 (n=37) | Group 2 (n=42) |
|---|----------------|----------------|
| Sudden death | 8 (21.6%) | 0 |
| Death from progressive heart failure | 5 (13.5%) | 0 |
| Hospital admission for progressive heart failure* | 13 (35.1%) | 4 (9.5%) |
| Total number of cardiac events | 19 (51.4%) | 4 (9.5%) |

Values are n (%).

*In group 1, two patients were admitted to hospital for progressive heart failure who later died suddenly out of the hospital, and five died from progressive heart failure while in hospital.

New York Heart Association (NYHA) functional classification, ejection fraction by radionuclide angiography at entry, or drug treatment for chronic heart failure. Differences were observed in echocardiographic features, ¹²³I MIBG imaging, and plasma noradrenaline concentrations: end diastolic left ventricular dimension ($p = 0.016$), left atrial dimension ($p = 0.034$), and plasma noradrenaline concentrations ($p = 0.001$) were all significantly greater in group 1 than in group 2. H:M ratio on the delayed image ($p < 0.001$) and washout rate ($p < 0.001$) were also significantly different between the two groups (table 1).

FOLLOW UP OUTCOME

Follow up was complete in all patients. The mean length of follow up was 31 months, with a maximum of 52 months. All the patients were examined at least once a month in our hospital during the study period. During that period, 23 of 79 patients (29.1%) had cardiac events. In group 1, eight patients died suddenly and five died of worsening heart failure. Thirteen patients were admitted to hospital for progressive heart failure (two of whom died suddenly out of the hospital and five subsequently died of worsening heart failure in hospital). By contrast, in group 2 no patient died of cardiac disease, although four were admitted for worsening heart failure (table 2).

Morbidity and mortality curves for the two groups are shown in fig 1. The two graphs show that both morbidity and mortality were significantly higher in group 1 than in group 2, using

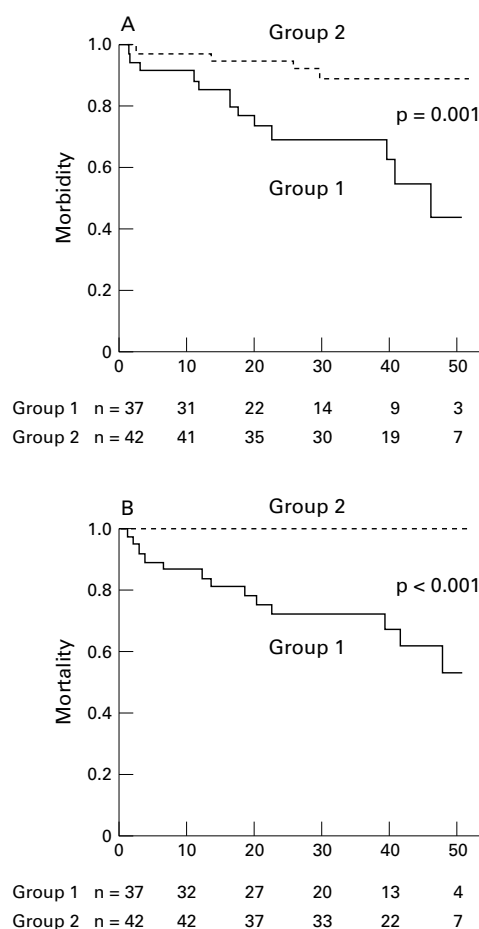


Figure 1 Comparison of morbidity and mortality curves between groups 1 and 2. Group 1 contained 37 patients whose cardiac MIBG washout rate was 27% or more. Group 2 contained 42 patients whose cardiac MIBG washout rate was less than 27%. Both morbidity (A) and mortality (B) were significantly higher in group 1 than in group 2 ($p = 0.001$ and $p < 0.001$, respectively).

the log rank test. Analyses of the ischaemic heart disease and non-ischaemic heart disease subgroups also showed that morbidity and mortality were significantly higher in group 1 than in group 2 in each subgroup (figs 2 and 3).

RETROSPECTIVE ANALYSIS OF PROGNOSTIC VARIABLES

At the end of the study, we were able to show that end diastolic left ventricular dimension, left atrial dimension, plasma noradrenaline concentrations, and heart to mediastinum ratio on delayed cardiac MIBG imaging, and ¹²³I MIBG washout rate were all significantly different between the two groups. We therefore performed a multivariate analysis to determine which of these indicators contributed most to morbidity and mortality in a Cox proportional hazards model. Only the washout rate could be shown to make a significant contribution to morbidity and mortality ($p = 0.034$ and $p = 0.028$, respectively) (table 3).

Discussion

PATHOPHYSIOLOGICAL CONSIDERATIONS RELATING TO CARDIAC MIBG WASHOUT

The uptake and release mechanism of ¹²³I MIBG is analogous to that of noradrenaline.

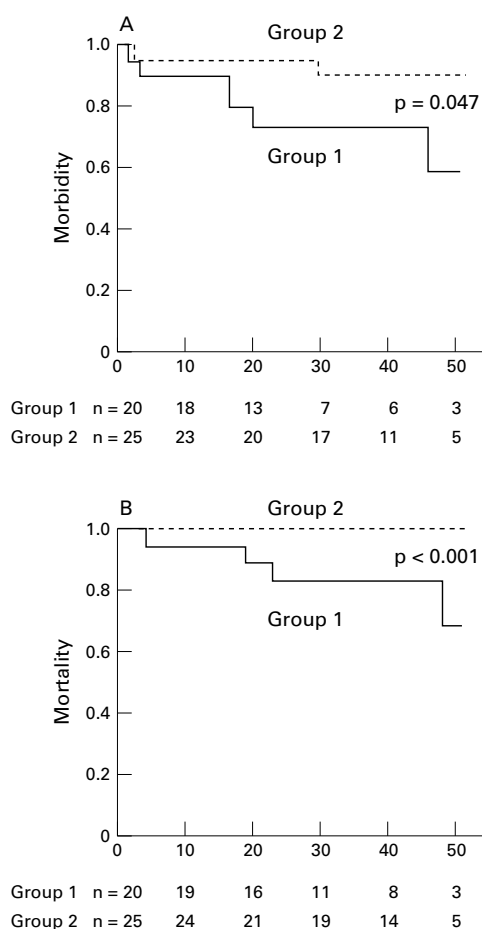


Figure 2 Comparison of morbidity and mortality curves in the ischaemic heart disease subgroup. Group 1 of this subgroup contained 20 patients and group 2 contained 25 patients. Both morbidity (A) and mortality (B) were significantly higher in group 1 than in group 2 ($p = 0.047$ and $p < 0.001$, respectively).

Two types of ^{123}I MIBG uptake systems have been identified—neuronal and extraneuronal.^{12,13} The low doses of ^{123}I MIBG used in clinical applications are thought to enter the cardiac adrenergic nerve cells mainly through the neuronal uptake system.¹⁴ Though ^{123}I MIBG and noradrenaline share a common mechanism of release into the adrenergic nerve synapse,¹⁵ ^{123}I MIBG, in contrast to noradrenaline, is not metabolised by catechol-*o*-methyltransferase and monoamine oxidase.¹⁶ Thus cardiac ^{123}I MIBG images appear to reflect the uptake and the release of noradrenaline.^{17,18} In chronic heart failure, myocardial retention of ^{123}I MIBG is significantly reduced, and as a result cardiac MIBG washout rate is increased. There are conflicting data on the

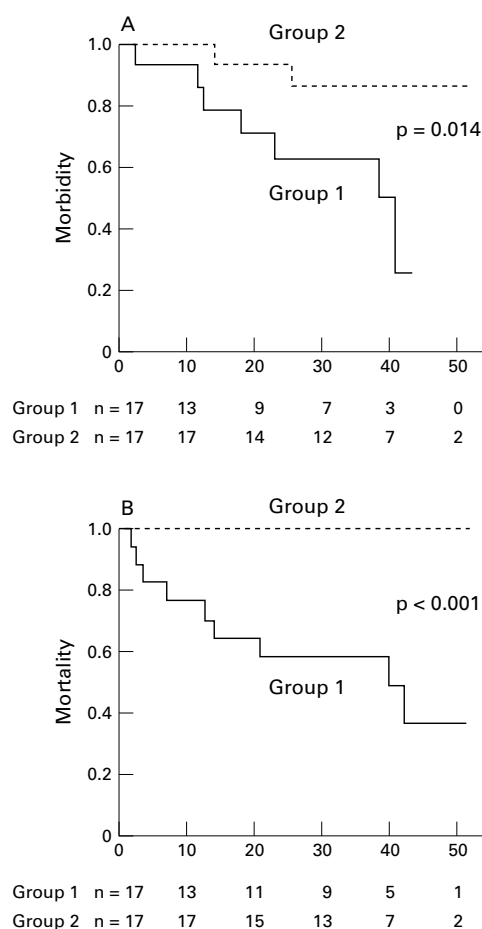


Figure 3 Comparison of morbidity and mortality curves in the non-ischaemic heart disease subgroup. Both group 1 and group 2 of this subgroup contained 17 patients. Both morbidity (A) and mortality (B) were significantly higher in group 1 than in group 2 ($p = 0.014$ and $p < 0.001$, respectively).

relative prognostic value of the MIBG washout rate versus the H:M ratio on delayed cardiac MIBG imaging.^{7,19} In this prospective study, we showed that the cardiac ^{123}I MIBG washout rate predicted morbidity and mortality in patients with chronic heart failure and a low ejection fraction. Though the H:M ratio on delayed imaging was significantly lower in group 1 than in group 2, multivariate Cox hazard analysis showed that only the washout rate contributed to the estimation of prognosis (table 3).

RELATION BETWEEN CARDIAC FUNCTION AND CARDIAC MIBG WASHOUT RATE

There are several reports that left ventricular ejection fraction and echocardiographic data are useful predictors of outcome in patients with chronic heart failure.^{20,21} However, in the present study we found no significant difference between group 1 and group 2 with respect to left ventricular ejection fraction. Although echocardiographic features of heart failure (end diastolic left ventricular dimension and left atrial dimension) were significantly increased in group 1 compared with group 2, on multivariate analysis these were not found to contribute to estimation of morbidity and mortality in our patients (table 3). There are various possible

Table 3 Multivariate analysis using the Cox proportional hazard model

| | Morbidity | | | Mortality | | |
|------------------------------|---------------|-----------------|---------|---------------|-----------------|---------|
| | Relative risk | 95% CI | p Value | Relative risk | 95% CI | p Value |
| LVDd (mm) | 1.018 | 0.952 to 1.089 | 0.606 | 1.084 | 0.995 to 1.181 | 0.066 |
| LAD (mm) | 1.032 | 0.968 to 1.100 | 0.334 | 0.968 | 0.885 to 1.058 | 0.467 |
| Plasma noradrenaline (pg/ml) | 1.000 | 0.998 to 1.002 | 0.981 | 1.001 | 0.998 to 1.003 | 0.654 |
| H:M ratio on delayed image | 1.217 | 0.117 to 12.695 | 0.870 | 2.851 | 0.126 to 64.646 | 0.511 |
| Washout rate (%) | 1.052 | 1.004 to 1.102 | 0.034 | 1.076 | 1.008 to 1.149 | 0.028 |

CI, confidence interval; H:M, heart to mediastinum; LAD, left atrial dimension; LVDd, left ventricular end diastolic dimension.

reasons why the cardiac MIBG washout rate, which reflects cardiac adrenergic nerve activity, should be a more sensitive indicator than cardiac function in assessing morbidity and mortality. Steady state measurements of cardiac function may be unable to provide sufficient insight into the dynamic response of the heart to stress. Furthermore, as cardiac adrenergic nerve activity may support myocardial contractility, for a given low left ventricular ejection fraction, patients with higher plasma noradrenaline concentrations are likely to have a more severe derangement of intrinsic cardiac function. For these reasons, cardiac MIBG washout rate appears to be a better prognostic indicator in chronic heart failure patients.

RELATION BETWEEN PLASMA NORADRENALINE CONCENTRATION AND THE CARDIAC MIBG WASHOUT RATE

An inverse relation between plasma noradrenaline concentration and survival has been observed in patients with chronic heart failure.⁴ However, plasma noradrenaline concentration did not appear to be highly predictive of morbidity and mortality in our present study on multivariate analysis (table 3). This may be because plasma noradrenaline, which is derived from adrenergic nerve activity throughout the body, may not directly reflect cardiac adrenergic nerve activity. Myocardial tissue catecholamine concentrations on endomyocardial biopsy specimens are reported to be reduced in patients with chronic heart failure.^{22, 23} However, endocardial biopsy is an invasive procedure, and it is unknown whether the small specimens obtained at biopsy truly reflect the catecholamine concentrations in the heart as a whole. Taking these factors into account, cardiac ¹²³I MIBG washout rate should be a more useful way of evaluating cardiac adrenergic nerve activity in patients with chronic heart failure.

LIMITATIONS OF THE STUDY

There may be a problem in quantifying cardiac ¹²³I MIBG images. A large decrease in cardiac ¹²³I MIBG activity is known to occur in patients with severe chronic heart failure. This may introduce errors when drawing regions of interest manually on cardiac MIBG images from patients with chronic heart failure. In our present study, two independent observers drew the ROI. The interobserver variation in counts per pixel was within 1.2%. Thus errors introduced by drawing the ROI manually on the cardiac MIBG images are likely to be subtle.

During this study, the patients were receiving treatment with angiotensin converting enzyme inhibitors or β blockers, or both, which could affect cardiac ¹²³I MIBG uptake.^{24, 25} However, the number of patients being treated with these agents was not significantly different between the two groups (table 1). We therefore suppose that their influence on the outcome of the study is likely to be unimportant.

CONCLUSIONS

So far as we are aware, this is the first study to follow up patients with chronic heart failure prospectively to determine the significance of

cardiac MIBG washout rate. The major finding was that patients with an accelerated washout rate had a poor prognosis, whether their heart failure was related to ischaemic heart disease or to other causes, and whether or not they were on treatment with ACE inhibitors or β blockers.

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